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Benchmarking of a T-wave alternans detection method based on empirical mode decomposition

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ABSTRACT

Background and objective: T-wave alternans (TWA) is a fluctuation of the ST-T complex occurring on an every-other-beat basis of the surface electrocardiogram (ECG). It has been shown to be an informative risk stratifier for sudden cardiac death, though the lack of gold standard to benchmark detection methods has promoted the use of synthetic signals. This work proposes a novel signal model to study the performance of a TWA detection. Additionally, the methodological validation of a denoising technique based on empirical mode decomposition (EMD), which is used here along with the spectral method, is also tackled.

Methods: The proposed test bed system is based on the following guidelines: (1) use of open source databases to enable experimental replication; (2) use of real ECG signals and physiological noise; (3) inclusion of randomized TWA episodes. Both sensitivity (*Se*) and specificity (*Sp*) are separately analyzed. Also a nonparametric hypothesis test, based on Bootstrap resampling, is used to determine whether the presence of the EMD block actually improves the performance.

Results: The results show an outstanding specificity when the EMD block is used, even in very noisy conditions (0.96 compared to 0.72 for SNR = 8 dB), being always superior than that of the conventional SM alone. Regarding the sensitivity, using the EMD method also outperforms in noisy conditions (0.57 compared to 0.46 for SNR=8 dB), while it decreases in noiseless conditions.

Conclusions: The proposed test setting designed to analyze the performance guarantees that the actual physiological variability of the cardiac system is reproduced. The use of the EMD-based block in noisy environment enables the identification of most patients with fatal arrhythmias.

1. Introduction

The phenomenon of T-wave alternans (TWA), which is found on the surface electrocardiogram (ECG) as a periodic pattern given on an every-other-beat basis, is referred to the subtle variations of amplitude, waveform, and duration of the ST-T complex. Also named repolarization alternans, it has been found to be a clinical method to identify patients at risk for malignant arrhythmias and also as a marker for stratifying risk of sudden cardiac death (SCD) [1–3]. From a theoretical point of view, the problem statement for its characterization is easy and well defined, as it basically consists of finding a periodic pattern. Although plenty of computerized methods have been proposed so far [4–10], hardly any of them can be utilized because no gold standard has still been developed for methodological validation of alternans techniques. The reason is that these fluctuations mostly take on values of some few microvolts, which are invisible to human eye, thereby preventing the design of annotated databases.

This lack of gold standard has resulted in testing methods which rely on synthetic signals, usually designed as the addition of ECG, alternant wave, and noise [4–13], enabling proper TWA identification due to the actual knowledge of alternans features (waveform, alternant voltage, and location, among others). Among the different approaches, those which utilize both simulated ECG and

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noise are less prescribed because they provide unrealistic signals, unable to replicate the nonstationary conditions of a clinical environment. Further, the composition of signals with a TWA pattern in the full ECG duration constrains the study to a detection probability analysis.

In stratifying SCD risk, patients classified into a high-risk group are eligible to therapy. The treatment usually consists of implantable cardioverter defibrillator (ICD), a small device embodied in the chest under skin, which uses electrical pulses to control life-threatening arrhythmias. Therefore, the desirable feature of a stratifying method like alternans would be the identification of most patients that will experience ventricular tachycardia or ventricular fibrillation, and the exclusion of those who will not [14]. So regarding the performance of a method, the analysis of the detection probability (sensitivity) is not only relevant, but also the evaluation of false alarm (specificity), which is a subject of major concern because it causes misdiagnosis in patients with lower risk. So, in order to characterize the specificity of a method, a study of episodes detection should be conducted. For this purpose, rather than creating ECG with sustained TWA, i.e., with alternans in the full length ECG, we propose the inclusion of TWA sections of limited duration so that the detection study of random TWA bursts, both in length and location, will enable the specificity assessment.

In [15], a technique based on the empirical mode decomposition (EMD) [16,17] was proposed to prevent the negative effects of noise during TWA testing. Therefore, the method was designed to provide with a noise free estimate of the ST-T complex to be used as a preprocessing block of any TWA detection technique. It was examined along with the spectral method (SM) [18,19], though the test setting was designed with sustained TWA, achieving only the study of the sensitivity.

The contribution of the present work is twofold. First, to develop a method to study the performance of a TWA detection system in its wide extension, i.e., in terms of sensitivity and specificity. For this goal, we propose a signal model to compile a test setting which captures the actual dynamic of the cardiac system based on the following guidelines: (1) use of open source databases to enable experimental replication; (2) use of real ECG and physiological noise; (3) inclusion of randomized TWA episodes. Second, to accomplish the study of the specificity for the EMD-based method proposed in [15]. In this case, the SM is chosen as TWA detector because it is one of the most widely accepted algorithms. Its validity has been proven in a number of clinical studies [20] and it is currently implemented in commercial equipments for its use in the clinical routine.

The performance validation is carried here out from two standpoints. On the one hand, we use receiver operating characteristics (ROC curves) to survey the detection capability of the proposed scheme. Both sensitivity and specificity are also separately analyzed. At the same time, the method for validating signal processing blocks proposed in [21] is applied in this work. The method uses a set of statistics and nonparametric hypothesis test, based on Bootstrap resampling [22], to determine whether the presence of the preprocessing block actually improves the performance.

The remainder of this paper is organized as follows. Section 2 briefly introduces the methods used in this work to design the detecting TWA scheme, namely, EMD, SM, complexity descriptors, and the procedure for estimating the ST-T complex. Next, the overall block diagram of the detector is described in Section 3. In Section 4, the proposed signal model is developed and Section 5 presents the metrics and the statistical methods to test our system. The results are shown in Section 6 and some limitations of the work are provided in Section 7. Finally, the conclusions are derived in Section 8.

2. Brief review of signal processing techniques

2.1. Empirical mode decomposition

The EMD [16] is a signal processing technique which decomposes a signal into a set of oscillatory functions denominated intrinsic mode functions (IMF). Any IMF is obtained through a signal dependent method referred to as “sifting process”, whose purpose is to elicit a function which matches with the definition of IMF: Function with an equal number of extrema and zero crossings (or at most differed by one) with its envelopes, as defined by all the local maxima and minima, and being symmetric with respect to zero. Thus, the original signal $x[n]$ can be represented as the sum of IMFs

$$x[n] = \sum_{i=1}^{L} c_i[n] + q_L[n]. \tag{1}$$

The right hand side of the equation above consists of L IMFs and a residue signal, $q_L[n]$, which may be a constant, a monotonic slope, or a function with only one extremum. An IMF represents a simple oscillatory mode as a counterpart to the simple harmonic function used in Fourier analysis. We refer to $c_i[n]$ as the ith-order IMF, and by this convention, lower order IMFs capture fast oscillation modes while higher order IMFs typically represent slow oscillation modes. From a time-scale analysis viewpoint, lower order IMFs and higher order IMFs correspond to the fine and coarse scales, respectively.

2.2. Review of the spectral method

The SM [19] looks for an every-other-beat periodicity corresponding to the TWA pattern by processing the power spectral density in beat series obtained from the surface ECG. After delineating and separating the ventricular repolarization portion, the method works over a set of M consecutive ST-T complexes. We may thus denote the m-th ST-T complex as an N dimensional vector

$$\mathbf{x}_m = [x_m(0), x_m(1), \ldots, x_m(N-1)]^T. \tag{2}$$

Preprocessing the ECG for signal conditioning, such as linear filtering, baseline wander elimination, QRS detection and delineation, beat alignment and rejection, among others, is usually considered so as to ameliorate the TWA interpretation [4]. The resulting repolarization segments are then allocated into the $M \times N$ matrix

$$\mathbf{M} = \left[\mathbf{x}_0^T, \mathbf{x}_1^T, \ldots, \mathbf{x}_{M-1}^T\right]^T = [\mathbf{s}_0, \mathbf{s}_1, \ldots, \mathbf{s}_{N-1}]. \tag{3}$$

From a column-wise standpoint, the $M \times 1$ vector $\mathbf{s}_n = [s_n(0), s_n(1), \ldots, s_n(M-1)]^T$ contains the samples of M consecutive heartbeats collected at the same time latency n. This sequence is the so called beat series, and its power spectrum density function is used to find the TWA periodic pattern of 2 at the component of 0.5 cycles/beat (beatquency domain)

$$P_n(f) = \frac{1}{M}\left|\sum_{m=0}^{M-1} s_n(m) e^{-j2\pi fn}\right|^2 \tag{4}$$

for $n = 0, 1, \ldots, N-1$. The contribution of the whole ST-T segment is given by the aggregate spectrum

$$P(f) = \frac{1}{N}\sum_{n=0}^{N-1} P_n(f). \tag{5}$$

The K-score, also known as TWA ratio, determines the magnitude of the power spectrum at the alternans frequency over the noise

$$K = \frac{P(0.5) - \mu_{noise}}{\sigma_{noise}} \tag{6}$$

where $P(0.5)$ is the value of the aggregate spectrum (in Eq. (5)) at 0.5 cycles/beat, and μ_{noise} and σ_{noise} are the mean and the standard deviation of noise, which is estimated in an adjacent reference band close to the alternans frequency, typically around 0.4 cycles/beat. A K-score is taken as statistically significant when the alternans component exceeds three times the level of noise, i.e., $K > 3$.

2.3. Complexity descriptors

The spectral purity index [15,23] (SPI) is a very well suited parameter to measure complexity in oscillatory signals such as IMFs. In this work, we use the SPI to assess complexity in the EMD domain. The SPI is determined as

$$\mathrm{SPI} = \frac{m_2^2}{m_0 m_4} \tag{7}$$

where

$$m_i = \int_{-\pi}^{\pi} \omega^i S_x\left(e^{j\omega}\right) d\omega \tag{8}$$

being m_i the ith-order spectral moment of the power spectrum $S_x(e^{j\omega})$ of a given signal $x[n]$. The SPI is used to analyze whether a signal may be described by a single frequency. It reports values in the range [0, 1], where unity is attained for a pure sinusoid, which corresponds to the simplest mode when dealing with oscillatory signals. Conversely, lower SPI values are linked to more complex components. In biological systems, normal biomedical systems are considered very complex [24], so the SPI is used in this work to assess complexity in the EMD domain and separate normal components, usually more complex and less regular, from undesirable ones, which may be identified by a high SPI value. For further details on spectral moment determination, which leads to SPI computation, see [15,23].

2.4. ST-T complex estimation

The aim of the EMD-based method is to separate valid components of the repolarization segment from noise. It is known that the morphology of this section of the ECG is smooth, while noise is a component characterized by fast variations. We then adopt the following model for any ST-T complex, $x_m[n],\ 0 \le n \le N-1$:

$$x_m[n] = s_m[n] + v_m[n],\ 0 \le m \le M-1 \tag{9}$$

where $s_m[n]$ and $v_m[n]$ are signal and noise, respectively. As EMD decomposes a signal as a set of IMFs ordered from quicker to slower oscillations, we assume that higher order IMFs, i.e., the slower components, are signal. Thus, using EMD, we may express the repolarization segments as follows:

$$x_m[n] = \underbrace{\sum_{i=1}^{P-1} c_{m,i}[n]}_{\hat{v}_m[n]} + \underbrace{\sum_{i=P}^{L} c_{m,i}[n] + q_{m,L}[n]}_{\hat{s}_m[n]} \tag{10}$$

being $\hat{s}_m[n]$ and $\hat{v}_m[n]$ the estimates of signal and noise, respectively. P is the IMF order, which has to be determined so as to separate noise and signal. Let us remind that an IMF is considered noise when it shows a regular oscillating pattern, which may be assessed using the SPI parameter. The rules to get proper separation of signal from noise components are as follows:

1. Usually, lower order IMFs capture high frequency artifactual components. In our case, the first two IMFs $c_{m,1}[n]$ and $c_{m,2}[n]$ are very fast oscillating modes, so they are rejected as signal assuming that most of the noise is captured by them.
2. The residue $q_{m,L}[n]$ is considered as part of the signal because it is a smooth and low varying component. Therefore, it is chosen as part of the signal.

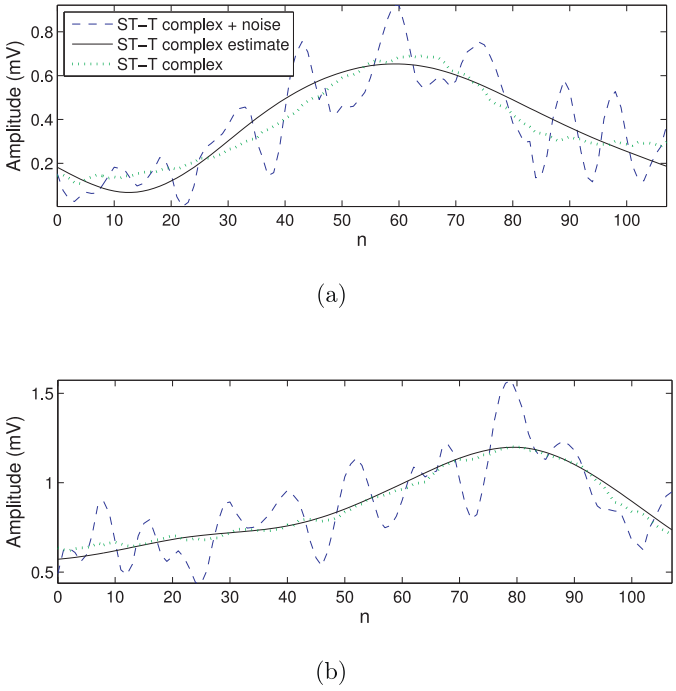

Fig. 1. Example of ST-T estimation for distinct signals from the MIT-BIH Arrhythmia Database. The original ST-T complex (dotted line) is corrupted by noise (dashed line), from which the ST-T estimate is determined (continuous line). (a) Record 103 and (b) Record 117.

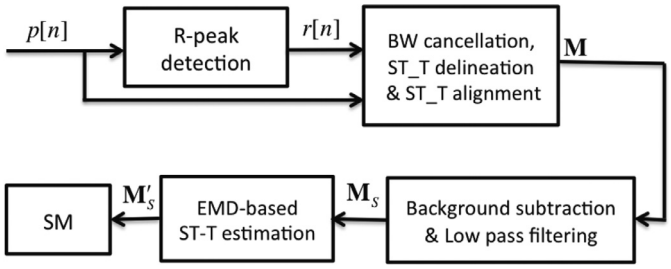

Fig. 2. Block diagram for the signal processing stages on the TWA detection system.

3. The residue itself does not fully define the ST-T complex, so additional IMFs (those that exhibit complex behavior) must be appended. Thus, starting from the L-th IMF toward lower order IMFs, the value of P is assigned to the first IMF considered to be noise, i.e., the one whose SPI is greater than a threshold ε.

In summary, the identification of IMFs is achieved by studying its complexity and taking IMFs components from higher to lower order until a regular and simple IMF is identified, being this one considered as noise. The process ends when this condition is reached, the signal being comprised of the P-th IMF up to the L-th one plus the residue: $\{c_{m,P}[n], c_{m,P+1}[n], \ldots, c_{m,L-1}[n], c_{m,L}[n], q_{m,L}[n]\},\ 2 < P \le L$. In this work, ε is set to be 0.7. Fig. 1 shows two examples of ST-T complex estimation taken from distinct signals of the MIT-BIH Arrhythmia Database [25]. Both panels depict the ventricular repolarization section of one heartbeat extracted from an ECG signal contaminated by physiological noise.

3. TWA detection framework

Fig. 2 depicts a diagram of the complete TWA detection system that operates over a sliding window length (M) of 128 beats with

Table 1
Dataset of control ECGs.

Record	Lead	V_{alt} (μV)
117	2	85
121	1	145
	2	65
122	2	75
123	1	55
	2	35

112 beats overlapping (D). Accordingly, $p[n]$ denotes an ECG signal window to be analyzed.

First, R-peak detection is accomplished by using the reference annotations associated to the database. A basic signal processing is done to adjust the fiducial points to the actual R-peaks. The output of this block ($r[n]$) is a vector containing the temporal positions of the R-peaks.

In the next block, baseline wander (BW) cancellation is first performed by third-order spline interpolation. Following, the ST-T complexes are segmented by taking a variable distance from the fiducial point, as proposed in [26]. Finally ST-T complexes are aligned as proposed in [27], a template is obtained as the median of 128 consecutive ST-T complexes and is used to align each ST-T complex by maximizing the cross correlation. The output of this block is an $M \times N$ matrix $\mathbf{M}$, where M is the number of beats and N is the number of samples of each ST-T complex.

In the following block, first the dynamic range of the alternant wave ε is increased by subtracting the background ECG, which is performed by subtracting consecutive rows in matrix $\mathbf{M}$ [28]. Next, a low pass filter is used to reject noise out of the TWA band (0.3–15 Hz) [4]. Therefore, the cutoff frequency is set to 15 Hz.

Next, EMD-based ST-T estimation (see Section 2.4) is performed starting from matrix $\mathbf{M}_S$. To end, TWA detection is performed by means of the SM (see Section 2.2).

4. Signal model

Benchmarking TWA methods cannot be easily accomplished due to the lack of annotated databases. Alternatively, the use of synthetic ECGs has been generally accepted [4–12] because they allow the TWA parameters to be known by artificially introducing alternans. In order to achieve a realistic setting to perform the evaluation of the proposed method, we propose to deal only with real signals. Additionally, for the sake of reproducibility, the actual ambulatory ECGs should only be taken from open source databases. In our case, we use signals from Physionet [25]. Thus, the strategy employed here consists of inserting TWA and noise into control ECGs.

The SM is currently the most accepted method to analyze alternans. Among the reasons for that, it is one of the early techniques developed for this purpose [29], but foremost, among the many clinical studies carried out within the scope of TWA, the vast majority have relied on the SM as the means to find alternans [20]. As this work seeks to determine whether an EMD-based method for estimating the ST-T complex is feasible when used along with the SM to detect TWA, we use the SM as a trusted method to design a dataset of ECGs free from TWA.

4.1. Simulated TWA in real ECGs

Control ECGs are collected from the MIT-BIH Arrhythmia Database ($f_s = 360$ Hz) according to the following criteria: (1) a signal is regarded as candidate only if more than 99% of its heartbeats are annotated as "*normal*"; (2) from candidates, only those without TWA are considered. The first two columns of Table 1 shows the ECG recordings that, according to our methods, have been defined to be control. The dataset consists of a total of 6 ECG signals taken from 4 records. To describe the signal model, we refer any of these control ECGs with the variable $p_c[n],\ 0 \le n \le L_p - 1$, where L_p takes on the value of the full ECG length, say 650,000 samples (about 30 min).

Physiological noise from the MIT-BIH Noise Stress Test Database [25] is also used to obtain ECGs with different signal-to-noise ratio (SNR). The simulations are performed combining muscular activity artifact, which is predominant in record '*ma*', and electrode motion artifact in record '*em*'. Noise is obtained as follows: (1) after lowpass filtering (FIR with cutoff frequency set to 4.75 Hz) to obtain zero mean realizations (by baseline drift cancellation), the 2 noise series contained in each record are first normalized with respect to its variance and subsequently concatenated; (2) the resulting '*ma*' and '*em*' noise records with unit variance are then combined into one single physiological noise record denoted as $v[n],\ 0 \le n \le L_v - 1$ ($L_v = 2 \times L_p$ samples). From $v[n]$, a noise realization segment $v_s[n]$ is randomly extracted:

$$v_s[n] = \begin{cases} v\left[\left((n - \lfloor \xi(s) \cdot L_v \rfloor)\right)_{L_v}\right], & 0 \le n \le L_p - 1 \\ 0, & \text{remaining} \end{cases} \tag{11}$$

where ξ is the uniform random variable $U(0, 1)$, $\lfloor \cdot \rfloor$ stands for rounding to the smallest integer, and $((A))_B$ denotes A modulo B. This operation takes on the first L_p samples of the noise realization $v[n]$ after random rotation. A noisy ECG may then be obtained as:

$$p_v[n] = p_c[n] + \beta \cdot v_s[n] \tag{12}$$

where β is a scaling parameter employed to obtain ECGs at different SNRs.

The alternant waves used in this study were estimated from an ECG with clear TWA recorded during a percutaneous coronary intervention, from the dataset used in [30]. These 15 waves are smoothed and resampled to fit the control ECGs with $fs = 360$ Hz. To obtain ECGs with TWA, an alternant waveform is added to the ST-T section of every-other-beat of the signal. Its amplitude is established by a function g_k, where k refers to the k-th heartbeat

$$g_k = \begin{cases} \alpha, & k \text{ even} \\ 0, & k \text{ odd.} \end{cases} \tag{13}$$

Thus, let $\varepsilon[n],\ 0 \le n \le L_\varepsilon - 1$, be an alternant wave, where $L_\varepsilon \ll L_p$, the resulting ECG for testing is

$$p[n] = p_v[n] + \sum_{k=1}^{N_h} \psi[k] \cdot g_k \cdot \varepsilon[n - n_k - n_J] \tag{14}$$

where N_h stands for the number of R peaks of $p_c[n]$. Parameter n_k denotes the ST-T onset of the k-th beat and time delay n_J introduces a jitter effect, which is characterized as a zero mean Gaussian random variable with a standard deviation corresponding to 20 ms. The function $\psi[k]$ is defined in the beat series domain as a composite window function constructed by concatenating simple window functions $w_j[k]$, as follows,

$$\psi[k] = \sum_{j=1}^{Q} w_j[k - k_j] \tag{15}$$

where Q stands for the number of concatenated windows whose length are N_j. The purpose of this function is to obtain Q alternans episodes in $p[n]$.

4.2. Experimental database

In order to perform the evaluation experiments, for each SNR, we generated a database of 100 records. Following we describe the procedure to obtain each of these records:

1. The control ECG ($p_c[n]$ taken from Table 1) is randomly chosen according to a uniform distribution.
2. The physiological noise segment ($v_s[n]$ of Eq. (11)) is extracted beginning at a random position in the complete noise record and added to $p_c[n]$ according to Eq. (12).
3. The alternant wave ($\varepsilon[n]$) is also randomly selected and added to $p_c[n]$ according to Eq. (14).
4. The insertion point of $\varepsilon[n]$ in the ST-T segment varies according to a normal distribution with $\sigma = 20$ ms.
5. The alternant episodes are included as bursts and the number of bursts in a signal, Q in Eq. (15), is randomly selected between 1 and 4.
6. The length of each burst (N_j) is also randomly set between 64 and 128 beats.
7. The function $w_j[k]$ (Eq. (15)) is a Tukey window, which is used to simulate a progressively increasing alternant amplitude (g_k) at the beginning of the burst, as well as a decreasing g_k at the end of the burst. The ratio between the taper section with respect to the total length window has been chosen to be 0.4.
8. The insertion point of each burst in the signal, k_j in Eq. (15), is also randomly selected.
9. The amplitude of the alternant waves for each control ECG (third column of Table 1) is set to be the lower voltage which yields a detection probability of 1 with sustained TWA using the SM, since it is the reference method in this study. Here the detection probability is determined as the ratio between correct detections (number of K-scores greater of 3) and the total number of computed K-scores.

With this elaborated procedure we obtain a database with a very high variability to evaluate the performance of the method.

5. Performance assessment

5.1. Objective metrics

Regarding the alternant wave voltage (Table 1), when inserted as in Eq. (13), it is defined as:

$$V_{alt} = \max\{|\varepsilon[n]|\}, \quad n = 0, \ldots, L_\varepsilon - 1, \tag{16}$$

The quality of $p[n]$ (14) is assessed by means of the SNR

$$\mathrm{SNR} = 10 \cdot \log \frac{\sum_n p_a^2[n]}{\sum_n (\beta v[n])^2} \tag{17}$$

where $p_a[n] = p_c[n] + \sum_{k=1}^{N_h} \psi[k] \cdot g_k \cdot \varepsilon[n - n_k - n_j]$ is a clean ECG containing TWA.

To evaluate the performance, we use the sensitivity, which assesses the probability of a TWA event being detected,

$$Se = \frac{TP}{TP + FN} \tag{18}$$

where TP and FN stand for true positive and false negative, respectively. The analysis of false alarm is addressed by means of the specificity, which determined the probability of a non-existent TWA event being detected,

$$Sp = \frac{TN}{TN + FP} \tag{19}$$

where TN and FP stand for true negative and false positive (wrong detections), respectively.

Fig. 3 shows the K-score resulting from a TWA analysis performed over a signal $p[n]$. The two curves of the upper panel (Fig. 3a) correspond to the SM with and without the EMD-based ST-T complex estimator, given as a function of the signal window over which the SM operates. There is one single K-score per segment. The lower panel (Fig. 3b) displays the same result but now

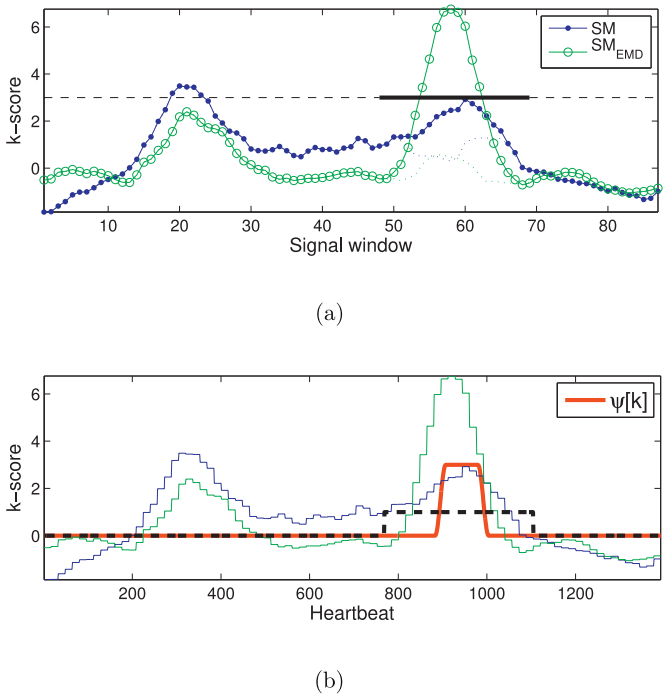

Fig. 3. TWA analysis performed over the first lead of recording 123 at SNR=12 dB with and without the EMD-based ST-T complex estimator. (a) K-score as a function of the signal window and (b) K-score as a function of the heartbeats.

in the beat domain, so here we can appreciate the window function $\psi[k]$ of Eq. (14) (thick continuous line) that is used to insert alternans, which in this case contains a single TWA episode. Even though the Tukey window around the 950-th heartbeat delimits the area where the alternant wave is included, the interval to which a TWA can be found is wider (thick dashed line) due to the effect of the sliding window.

As the experiment in this work is concerned with the detection of TWA episodes, we will consider that an alternans episode has been recognized if at least 2 consecutive K-scores have been found to be significant, namely, $K > 3$. The reason is that one positive K-score means that a TWA is found as a result of the analysis of a signal window of $M = 128$ heartbeats. The next positive K-score means that the next signal segment of 128 heartbeats, where $D = 112$ beats are shared with the previous segment while 16 news are incorporated, still elicit positive TWA. In the example of Fig. 3a (upper panel), there are three sections where one of them, labeled with the thick horizontal line, highlights the TWA burst. So, according to the criterion defined earlier, with the SM alone (continuous curve with dots), the resulting statistics are: $TP = 0$, $FN = 1$, $TN = 1$, $FP = 1$. When including the EMD-based block to perform detection (continuous curve with circles), we obtain: $TP = 1$, $FN = 0$, $TN = 2$, $FP = 0$.

5.2. Bootstrap resampling

In this section, a Bootstrap resampling scheme, already presented in [21], is used in the evaluation of the performance differences between the EMD-based method and the SM.

We can study sampling variability by sampling by an artificial population, for example this artificial population can be the dataset from which we seek to draw inferences. Since the dataset is itself a sample of the whole population, we are taking a sample from the sample, i.e. resampling. This does not provide more information from the population, but it does provide us with a way of understanding the consequences of sampling variability for drawing

inferences about the population based on our data. The resampling method can be used to compute the confidence interval (CI) of many different types of statistics and to perform hypothesis testing [31].

In the present problem we need to decide whether the performance differences between EMD-based method and the SM are statistically significant in terms of a given performance statistic.

Our statistical hypothesis test will contrast the null hypothesis (H_0) that both methods have the same performance, against the alternative hypothesis (H_1) that they have different performance. Let u_{SM} and u_{EMD} denote the performance statistic obtained for each method. Then, the hypothesis test can be stated as

$$H_0 : \Delta u = 0$$
$$H_1 : \Delta u \neq 0 \tag{20}$$

where $\Delta u = u_{EMD} - u_{SM}$.

In order to approximate the probability density function (pdf) of u_{SM}, u_{EMD}, and subsequently of Δu, we use the well-known plug-in principle. In brief, let $Z = \{z_j, j = 1, \ldots, L\}$ be a set of L measures, and let u be a statistical magnitude estimated by using an operator O on the observed set, i.e., $u = O(Z)$. Since actual $f_Z(Z)$ is unknown and only a finite number of samples are available, and operator O can be complex, then $f_u(u)$ will be often impractical to compute. Alternatively, we can approximate $f_Z(Z)$ for its plug-in empirical distribution. We build sets $Z^*(b)$ (so-called resamples from Z), by sampling with replacement up to L elements of Z. Now, a replication of statistic u is obtained as $u^*(b) = O(Z^*(b))$, and it represents an estimate of this statistic. By repeating the resampling procedure for $b = 1, \ldots, B$, an estimated *pdf* is given by

$$\hat{f}_u(u) = \frac{1}{B}\sum_{b=1}^{B} \delta(u - u^*(b)). \tag{21}$$

An estimation of the CI for Δu, can be readily obtained from ordered statistics in $\Delta u^*(b)$ resamples [22]. The differences between the two methods are statistically relevant in terms of statistic u when the 95% IC of Δu does not overlap the zero value.

In the present problem of TWA detection, Z stands for *TP, FP, TN* and *FN* measures, and u stands for specificity (Sp) and sensibility (Se).

We start from two matrices of size 100×4, each row contains the *TP, FP, TN, FN* values of each signal $p[n]$ (see (14)), one for each TWA detection method (*SM* and *EMD*). In each resampling iteration these matrices are resampled with replacement, paired and row-wise, this is, all the measures from one single signal remain together. The Sp and Se values are computed in each iteration. At the end of B iterations an estimation of the pdfs for the Sp and Se are obtained for the SM (Sp_{SM}, Se_{SM}) and for the EMD-based method (Sp_{EMD}, Se_{SM}), and the estimations of the pdfs for ΔSp and ΔSe are obtained as

$$\Delta Sp = Sp_{EMD} - Sp_{SM}$$
$$\Delta Se = Se_{EMD} - Se_{SM}. \tag{22}$$

In our experiments the number of resamplings is set to $B = 1000$.

Fig. 4 shows an example of the estimated pdfs for ΔSe and ΔSp represented as histograms, the 95% CI is represented with bars. If the CI does not contain the zero the differences between the SM and the EMD-based method are statistically significant. The top panel shows that differences in Se are not significant, but Sp (bottom panel) is significantly higher for the *EMD* method.

6. Results

As the proposed method has been originally conceived to counteract the effect of noise, the system is analyzed in two environments: at an SNR of 8 dB, which represents severe noisy conditions, and at 28 dB. ROC curves, displayed in both the upper graphs

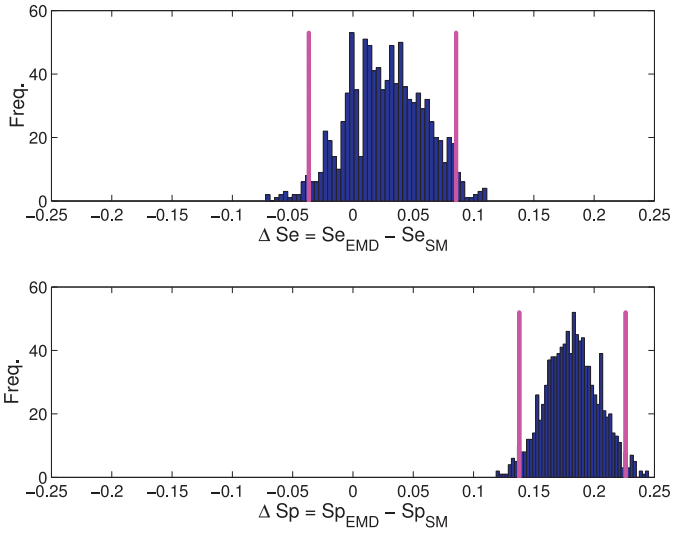

Fig. 4. Estimated pdfs for ΔSe (top) and ΔSp (bottom), the 95% CI is represented with bars, SNR = 12 dB.

of Fig. 5, are obtained by computing Se and Sp at different significance level, i.e., using different threshold values to elicit a significant K-score. In noisy milieu (Fig. 5a), the area under the curve (AUC) is greater when the EMD block is used (0.82 against 0.63), being approximately the same as that of the SM when the amount of noise is irrelevant (top (Fig. 5b). This behavior indicates that the detectability improves in noisy environments.

For a closer understanding, we may separately examine Se and Sp, depicted in lower graphs of Fig. 5. At this point, the attention is drawn to a threshold value equal to 3 because this is the significance level taken by the K-score in clinical practice. We may see that the specificity is outstanding when the EMD block is used, even in the noisy case ($Sp_{EMD} = 0.96$ against $Sp = 0.72$), being always superior than that of the regular SM method. Regarding the sensitivity, using the EMD method also outperforms in the noisy case, while it decreases in noiseless conditions.

The performance evaluation scheme presented in Section 5.2 confirms the statistical significance of the presented results. Fig. 6 shows the estimated pdfs for ΔSe and ΔSp at SNR = 8 dB (Fig. 6a) and SNR = 28 dB (Fig. 6b). The Sp is significantly better when the EMD block is used at both SNR values. The Se is also significantly better using the EMD method in noisy conditions, whereas it is significantly worse in low noise conditions.

7. Discussion

TWA has been found to be a predictor of SCD, so it is used in many studies as a potential method for stratifying risk. Therapy against SCD is traumatic because it requires to insert an ICD under surgery, so the characterization of false alarm is crucial to avoid misclassification of low risk patients into a higher risk group. Therefore, the validation of a stratifying method requires studying not only the sensitivity but also its specificity. TWA is one of the many indices suggested as SCD marker from the ECG signals [1,32,33], and a recent review can be found in [34] about patients at risk for insertion of prophylactic ICDs. Recent studies continue to emphasize the relevance of TWA as SCD marker. For instance, several risk markers were jointly benchmarked in [35] (including TWA, heart rate turbulence, and ectopy) for evaluating the risk of standard vs daily hemodyalisis procedures, in which TWA was sensitive enough to show a trend to change in the second one. In a recent study [36], the SCD risk was evaluated using the modified

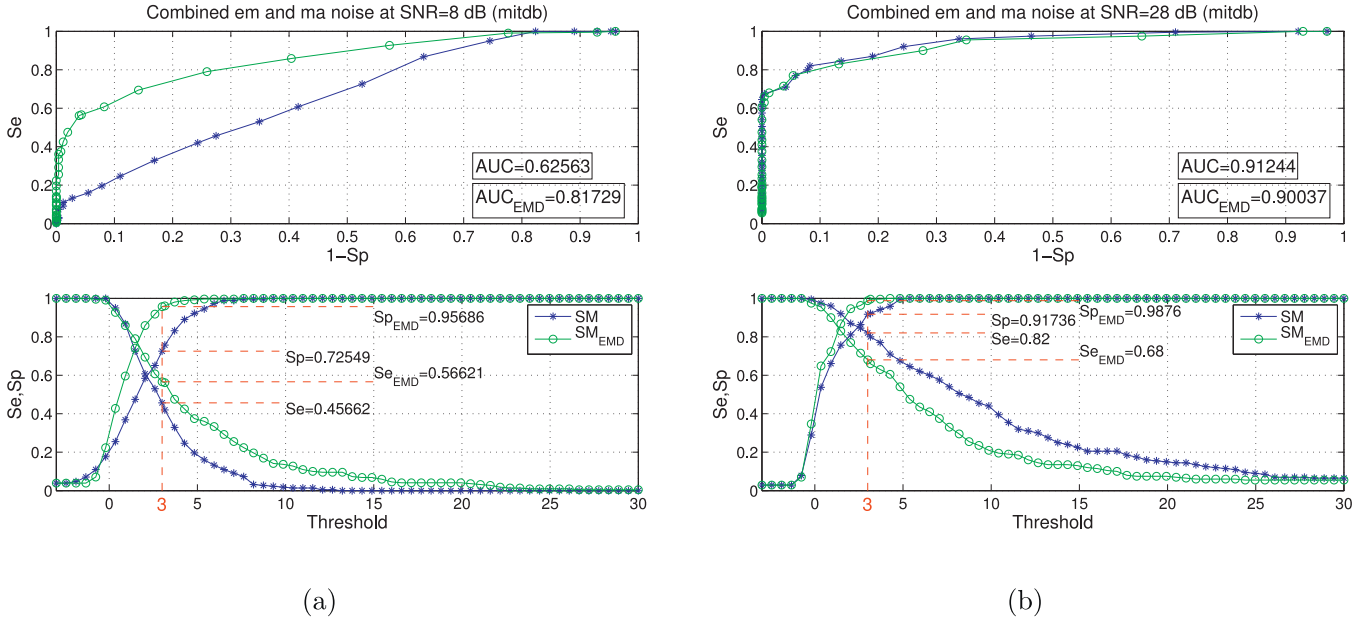

Fig. 5. ROC curves (upper graphs) and *Se* and *Sp* curves (lower graphs) against the significance level. (a) SNR = 8 dB and (b) SNR = 28 dB.

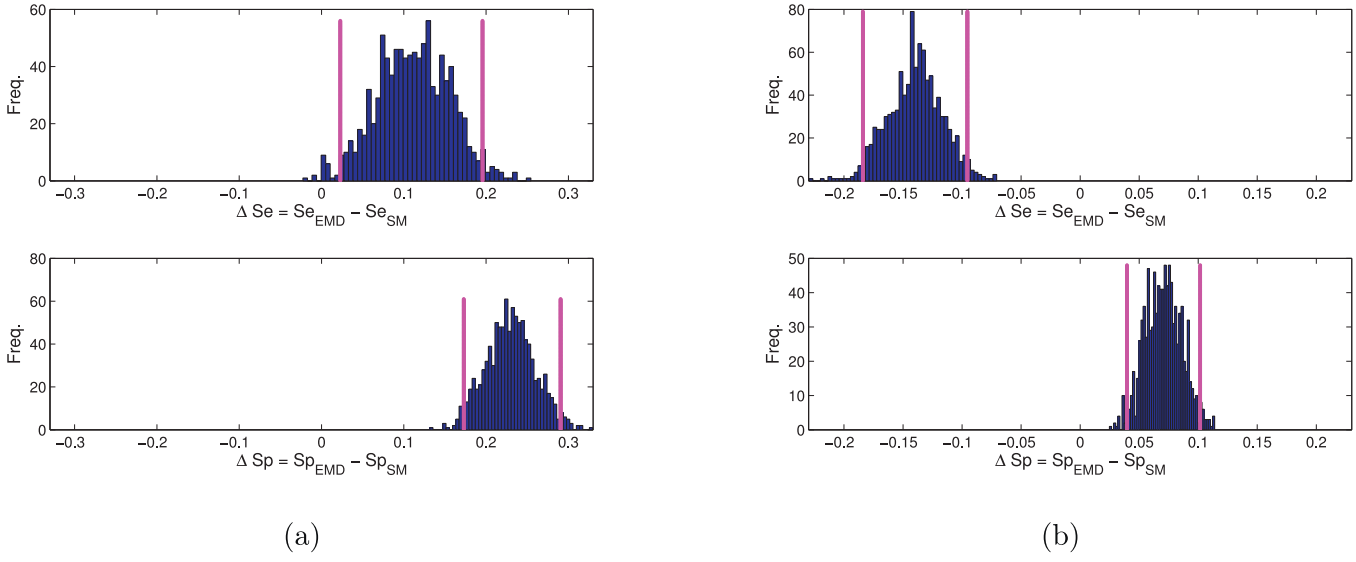

Fig. 6. Estimated pdfs for ΔSe (upper graphs) and ΔSp (lower graphs), the 95% CI is represented with bars. (a) SNR = 8 dB and (b) SNR = 28 dB.

moving average (MMA) method also for patients with hypertrophic cardiomyopathy, showing a trend for TWA increasing with risk.

Another source of false alarm is the noise affecting the original data. This is because the process by which the signal is gathered during a TWA test generates ECGs with high levels of artifacts. In [37], multi-level noise signal quality classification was made, and special attention was paid to merit figures, such as accuracy, sensitivity, and specificity, in which the clinical relevance of the noise was scrutinized with detail for general ECG diagnostic applications. More, given that predictive alternans is a heart rate dependent phenomenon, exercise testing is one of the most extensively used procedure to elevate the cardiac rhythm. Alternatively, the analysis in ambulatory ECG records is currently yielding promising results [1]. Anyway, either of these methods records the ECG with patients in continuous movement. Thus, the study of TWA detection methods under strong noise conditions is necessary to determine whether a method is robust against artifacts. Aiming for a wider clinical usefulness of TWA, the MMA method has been often suggested as a robust method for TWA measurement in long-term monitoring. In [38], the enhanced modified average method and the correlation method were compared for microvolt TWA identification in simulations and ECG recordings, by analyzing healthy subjects and patients who had survived acute myocardial infarction. The correlation method seemed to follow better nonstationary, and also the enhanced approach trended to give a larger number of false-positive TWA detection.

Toward this direction, a set of novel experiments that uses only real ECG signals is proposed here to carry out the validation. Briefly, the experimental test consists of detecting burst of TWA randomly included in actual ECGs corrupted by physiological noise. The design of this test bed in this way guarantees that the actual physiological variability of the cardiac system is reproduced. Additionally, this work analyzes the performance of an ST-T complex estimation method based on the empirical mode decomposition, originally conceived as a preprocessing block of a TWA detector. The purpose of this block is to let the detector be able to deal

with noise and artifact. Here the block is inserted as part of the spectral method, which was chosen because it is one of the most extensively used. Thus, the analysis of the EMD-based technique operating as a preceding block of a qualified method that is used in clinical routine will support our study.

The results are obtained following two methodologies: (1) examination of ROC curves and (2) hypothesis testing based on Bootstrap resampling. From their analysis, we can state that the use of the preprocessing block always reports superior performance in terms of specificity, resulting in fewer false positives. On the other hand, the detection probability (Se) outperforms in noisy environment, which is mostly the situation under which the analysis of TWA is usually performed. According to these results, we can claim that the introduction of the EMD block makes the system more robust due to the specificity growth, but this advance comes at the expense of a sensibility reduction in artifact free conditions. Although this is not the regular situation during a TWA test, the improvement of the sensibility for noise free ECG is an issue to be addressed in future investigations. Currently we are exploring the use of advanced EMD methods to enhance detection.

It is known that one problem of the EMD is the mode mixing phenomenon, so other recent EMD versions have been developed to alleviate this issue, such as for example the Ensemble EMD (EEMD) [39]. Under the hypothesis that the simple replacement of the EMD by a more advanced version would outperform the current results, we have developed preliminary experiments with EEMD achieving the following findings. First of all, as EEMD is based on averaging the resulting IMFs obtained from iteratively applying EMD to the signal plus additive noise, it is not computationally comparable with EMD. Particularly, using EEMD has increased the computational time from approximately 2 min to more than 1 h (25 runs for IMF averaging) up to 6 h (100 runs). Furthermore, the use of the EEMD does not yield a clear improvement over the EMD, because the reported K-score values are less regular and they exhibit higher variability. Our consideration is that the simple substitution of the EMD without altering the set of IMFs selection rules of Section 2.4 is not sufficient and that the application of other EMD techniques deserve deeper observation and studies to develop specific methods to process IMFs. Nevertheless, the EEMD method has been suggested as a direction for providing with enhanced classification in beat-to-beat TWA detection from ECG signals, as pointed out in [40] for simulated signals and for a patients database.

In any case, there is a strong interest in medical studies based on TWA markers. In [41], a simulation study on TWA was created by changing the duration of the ventricular heart cells action potentials, and the magnitude in the surface ECG was obtained with the time domain method. The presence of spatially concordant TWA was scrutinized with the vectorcardiographic representation, aiming to explain its spatial heterogeneity. In [42], the instability in the atrial repolarization process recorded in the ECG was investigated, by using an autorregressive and exogenous model both in sinus rhythm and in patients with atrial tachycardia. In [43], authors studied the capacity of the novel cardiac late sodium inhibitor eleclazine in suppressing catecholamine-induced ventricular tachycardia, and in reducing T-wave alternans in an animal model. These studies show that the trend will undoubtedly continue to require the accurate measurement of TWA towards new clinical scenarios, hence the false alarm rate should be controlled in the TWA measuring methods.

8. Conclusion

The introduction of the EMD-based block in combination with the spectral method reports an advance in the detection of TWA due to the specificity and sensitivity improvement for noisy conditions. Therefore, because a TWA test is applied over ECG signals with high content of artifacts, the use of the EMD block enables the identification of most patients with fatal arrhythmias, but not at the expense of the false alarm ($1 - Sp$) reduction.

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